REMARKS

I. Amendment of the Claims

Claim 43 has been amended to include the number of nucleotides in A, B, C and D as well as overall length of the oligonucleotide recited in claim 47, which has been cancelled. In addition to claim 47, claims 53, 55-58, 71-74, 82-85 and 88-96 are cancelled in this amendment. Claims 63-66 have been amended to recite an overall length of 12-18 nucleotide units rather than 12-21 nucleotide units. Support for this amendment is found in the specification, for example, on page 8, at line 29 (in the paragraph that begins starts "In the above constructs..."). No new matter has been added.

Upon entry of this amendment claims 43, 48-51, 59-70, 75-81, 86 and 87 will be pending, and claims 1-42, 44-47, 52-58, 71-74, 82-85, and 88-96 will be cancelled.

II. Advisory Action dated February 17, 2009

In the Advisory Action the Examiner stated that Applicant's assertion that the rejection of then pending 43, 47-51, 53 and 55-96 under 35 U.S.C. §103(a) "is based on routine optimization of what is disclosed in Wahlestedt is incorrect: the rejection is based in the combined teaching of Wahlestedt and Crooke." The Examiner went on to state that "[w]hile it is correct that the XYXY pattern claimed by applicants is not the only pattern contemplated by Wahlestedt, it is well known to those in the antisense art that the ability of an oligonucleotide to activate RNaseH is a critical consideration .... Wahlestedt teaches that non-oxy-LNA monomers can be used to purposely change the RNase H activity of oligionucleotides; this would clearly be done by changing the number of and position of the non-oxy-LNA monomers."

III. Response to the rejection of claims 43, 47-51, 53 and 55-96 under 35 U.S.C. §103(a)

In the recent Advisory Action the Examiner maintained the previous rejection of claims 43, 47-51, 53 and 55-96 under 35 U.S.C. § 103(a) as allegedly obviousness over Wahlestedt (WO 01/25248) in view of Crooke (US 5,898,031). Claim 43 has been amended to include the

number of nucleotides in A, B, C and D as well as overall length of the oligonucleotide recited in claim 47, which has been cancelled. Claims 53, 55-58, 71-74, 82-85 and 88-96 are cancelled. Applicant continues to traverse this rejection as it applies to the pending claims.

The Examiner has failed to clearly explain why the presently pending claims are *prima facie* obvious in view of Wahlestedt and Crooke.

The Examiner stated in the recent Advisory Action that Applicant's statement that the rejection is based "on routine optimization of what is disclosed in Wahlestedt" is incorrect and that the rejection is based on the combination of Wahlestedt and Crooke. However, in the Office Action dated July 9, 2008, the Examiner stated that "[b]ased on the well-known practice in the art of optimization, that is exemplified by Crooke, one of ordinary skill in the art would have been motivated to modify the invention of Wahlestedt et al. to produce antisense oligonucleotides wherein the individual segments have particular lengths in order to produce an oligonucleotides having the necessary degree of specificity and stability suitable for a particular application. (emphasis added)" Moreover, the Examiner cited MPEP 2144.05 (discussing obviousness of ranges and "optimization within prior art conditions or through routine experimentation") to support that proposition that "routine optimization of what is known in the prior art supports a *prima facie* case of obviousness" (emphasis added). In the same Office Action the Examiner stated that Crooke is relied on not to teach oligonucleotides acting by any particular mechanism, "but to demonstrate that the optimization of oligonucleotides length and structure was a mater of simple experimentation regularly engaged in by those in the art (emphasis added). Thus, it certainly appears that the obviousness rejection was previously based on the argument that one would arrive at the claimed oligonucleotides based on "routine optimization" of the oligonucleotides disclosed by Wahlestedt. If the Examiner maintains the obviousness rejection, Applicant respectfully request that the Examiner clearly articulate the basis for the rejection, in particular whether or not the rejection is based on "routine optimization" of what is disclosed in Wahlestedt.

Legal basis for a rejection under 35 U.S.C. §103

In order to make a proper rejection under 35 U.S.C. §103, the Examiner must first: (a) determine the scope and content of the prior art; (b) ascertain the differences between the claimed invention and the prior art; and (c) resolve the level of ordinary skill in the pertinent art. Once these factual underpinnings have been established, the Examiner must articulate why the claimed invention would be obvious to one of ordinary skill in the art. The rejection "cannot sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007). Moreover, the Examiner must provide "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." (*KSR* 550 U.S. at 407; see also *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (To established obvious of a chemical compound it is "necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner").

In the present case the Examiner has stated that the claimed genus is within a genus disclosed by Wahlestedt.

The "patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. 103" (MPEP 2144.08).[1] The MPEP explains that:

> In the case of a prior art reference disclosing a genus, Office personnel should make findings as to:
>
> (A) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus;
>
> (B) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus;
>
> (C) the predictability of the technology; and
>
> (D) the number of species encompassed by the genus taking into consideration all of the variables possible.

[1] It should also be noted that fact that a claimed subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness. *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992); *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995)

The MPEP then goes on the explain that: "Once the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus are identified, Office personnel should compare it to the claimed species or subgenus to determine the differences. Through this comparison, the closest disclosed species or subgenus in the prior art reference should be identified and compared to that claimed." (emphasis added). Next, the Examiner should determine whether one of ordinary skill in the art would have motivated to select the claimed species or subgenus. The MPEP lists a number of factors that should be considered in making this determination, including: the size of the genus, express teachings in the art, teachings of structural similarity, teachings of similar properties or uses, and the predictability of the art. MPEP 2114.08 (II) (A) (4). Finally, the Examiner "must make express fact-findings relating to the *Graham* factors, focusing primarily on the prior art teachings that specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus." MPEP 2114.08 (II) (A) (5).

The importance of identifying the closest disclosed species or subgenus at the outset of obviousness analysis was recently emphasized by the Federal Circuit in a case concerning the requirements for establishing a case of *prima facie* obviousness based on chemical similarity in the context of a pharmaceutical invention *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007). The court in *Takeda* held that order to establish a *prima facie* case in such a situation it is "necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner" and that "a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." *Takeda* at 1356-57 (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)) (emphasis added). Moreover, in *Takeda*, the court found that the argument for obviousness failed because it relied on selecting one of the many compounds disclosed in the prior art reference as a lead compound where there was reason to believe that the compound would not have been selected as the lead compound. *Takeda* at 1360. *See also Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals*, 471 F.3d 1369 (Fed. Cir. 2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as lead compound.

Here the Examiner has failed to carry out the proper analysis for at least three reasons: 1) the rejection is based on an undisclosed subgenus; 2) the undisclosed subgenus that is the basis for the rejection does not encompass the claimed oligonucleotides; and 3) there is no explanation regarding what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus. In view of this, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

The Examiner has improperly based the rejection on an undisclosed subgenus

In the present case, the Examiner began the obviousness rejection by stating that Wahlestedt "teaches oligonucleotides with the pattern X-Y-X-Y, meeting the limitations of the claims". As the Applicant explained previously Wahlestedt does not disclose such an oligonucleotide. The only species disclosed by Wahlestedt are limited to one having the pattern X-Y-X where all X are LNA (page 10, line 9) and Y-X-Y-X-Y-X-Y-X-Y, which all X are LNA (page 10, line 10). The only genus disclosed is by Wahlestedt is 5'-$[X_mY_nX_p]_q$-3' where "X is oxy-LNA and Y is non-oxy LNA", both m and p are integers from "0-30", "n is an integer from 0-3", and q is an integer from 1 to 10 and "the sum of m, n and p multiplied by q is in the range of 6-100."[2]

As explained above, an obviousness rejection must be based on a disclosed species or subgenus in the prior art reference. The Examiner has not done this. Instead, the Examiner has based the rejection on an undisclosed subgenus: XYXY. For this reason alone, the rejection is improper and should be withdrawn.

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[2] Applicant reminds the Examiner that the non-oxy-LNA are not equivalent to the non-LNA of the present claims. "Non-oxy LNA", represented by Y, are defined on page 4 of Wahlestedt at lines 4-12 as including DNA, RNA, thio-LNA and amino-LNA as well as derivatives of these molecules. Thus, the oligonucleotides within the genus described by Wahlestedt can be composed entirely of various types of locked nucleotides (LNA). Therefore, Wahlestedt's genus does not simply encompass various oligonucleotide having alternating locked and non-locked nucleotides, but actually encompasses a much larger universe of molecules that includes locked nucleotides that are not oxy-LNA. Thus, if Y nucleotides that are non-locked nucleotides of any type are represented by "Y" and those nucleotides that are locked nucleotides, but not oxy-LNA (e.g., are amino-LNA or thio-LNA) are represented by "**Y**", then Wahlestedt's genus encompasses, for example, X**Y**Y**Y**XY**Y**X, X**Y**, YX**Y**Y**Y**XYX, XY**Y**, **Y**X**Y** and a huge number of other patterns. Thus, it is incomplete to say that "antisense oligonucleotide having LNA an non-LNA segments wherein the LNA includes oxy-LNA and the non-LNA sequences are DNA, RNA and analogues."

The subgenus relied by the examiner does not encompass the presently claimed oligonucleotides

The subgenus relied on by the Examiner is not only not disclosed by Wahlestedt, but it does not even encompass the claimed oligonucleotides.

The Examiner previously stated that Wahlestedt teaches "antisense oligonucleotides having LNA and non-LNA segments wherein the LNA includes oxy-LNA and the non-LNA sequences are DNA, RNA and analogues." The Examiner also previously stated that "Wahlestedt teaches that the pattern of X-Y-X can be repeated, as indicated by the integer q, and that because the integers m and p can be 0, [Wahlestedt] teaches oligonucleotides with the pattern X-Y-X-Y, meeting the limitations of the claims." As explained above, X-Y-X-Y is not an disclosed subgenus, and thus cannot be used as the basis for an obviousness rejection. Moreover, even if it were disclosed, it could not be used as the basis for an obviousness rejection because it does not encompass the presently claimed oligomers, as explained in greater detail below.

Wahlestedt describes a genus of oligonucleotides characterized by the following formula: 5'-$[X_mY_nX_p]_q$-3'. In this formula "X is oxy-LNA and Y is non-oxy LNA" According to Wahlestedt, both m and p are integers from "0-30", "n is an integer from 0-3", and q is an integer from 1 to 10 with the *proviso* that the sum of m, n and p multiplied by q is in the range of 6-100. Thus, to arrive at the XYXY subgenus discussed by the Examiner, p would need to be 0 (resulting in the subgenus 5'-$[X_mY_n]_q$-3'), and q would need to be 2, resulting in the subgenus 5'-X_mY_n X_mY_n-3'. Thus, Wahlestedt teaches that the length of the oxy-LNA segments should be equal in length and the blocks non-oxy LNA should be of equal length. Thus, even if Wahlestedt disclosed the XYXY subgenus, which Wahlestedt did not, the subgenus would not encompass the oligonucleotides of the claims.

In addition, Wahlstedt teaches the length of non-oxy LNA (Y) portion to be 0-3 ("n is an integer from 0-3"), however the length of the corresponding region B in the oligonucleotides of present claim 43 is "of between 4-12".

Thus, even if Wahlestedt disclosed the XYXY subgenus, the Examiner's basis for this obviousness rejection is improper and should be withdrawn because the subgenus relied on does not encompass the claimed oligonucleotides.

The Examiner has not provided a reason for modifying Wahlestedt other than a general desire for optimization or alteration of RNase activity

As noted above, when rejecting a claimed subgenus or species in view of a prior art genus, the Examiner must "articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus."

The Examiner has failed to identify the teachings that would lead one skilled in the art to arrive at the presently claimed oligonucleotides. Instead, the Examiner appears to suggest that the presently claimed oligonucleotides would be arrived at through a general desire for optimization or alteration of RNase activity. The Examiner "must make express fact-findings relating to the *Graham* factors, focusing primarily on the prior art teachings that specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus." MPEP 2114.08 (II) (A) (5). The reasons cited by the Examiner are merely reasons to alter what is disclosed by Wahlestedt. They are not reasons that would lead one to arrive at the presently claimed oligonucleotides. Thus, the Examiner has not met the requirement that the "teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus" be articulated.

IV. Oligonucleotides within the present claims have unexpected advantages

As explained in the accompanying Declaration of Miriam Frieden, oligonucleotides within the present claims can have unexpected advantages. Specifically, by placing a DNA nucleotide rather than a LNA at the 3' end of a gapmer oligonucleotide having a stretch of DNA flanked by LNA, it is surprisingly possible to create an oligonucleotide that is more potent than an oligonucleotide of the same length and sequence, but containing more phosphothioate bonds.

Wahlestedt, at page 2, states that many antisense oligonucleotides "comprise a central region of at least six contiguous, low affinity phosphoshioates (RNase recruiting analogues) flanked by stretches of high affinity analogues (non RNase recruiting analogues)". The "gab-

mer" on page 10 of Wahlestedt is an example of such an oligonucleotide – 6 DNA nucleotides are flanked by 4 LNA at the 5' end and 5 LNA at the 3' end. Wahlestedt, at page 1, explains that DNA nucleotides have drawbacks in antisense oligonucleotides because they "exhibit only modest affinity for RNA and fall short on a number of the other critical characteristics, especially nuclease resistance." These teachings of Wahlestedt suggest that it would not be desirable to include DNA nucleotides at the 3' end of a molecule having stretch of DNA nucleotides flanked by LNA because the DNA nucleotide would have lower affinity for the RNA that and LNA and would be subject to attack by nuclease. In addition, given that Wahlestedt teaches that the nonoxy-LNA region ("Y") should be only 0-3 nucleotides, Wahlestedt teachings suggest that it would not be desirable to have a stretch 4-12 non-LNA (e.g., DNA), as required by the present. Thus, Wahlestedt suggests that it would not be desirable to have an oligonucleotide such as that in present claim 43. However, as the accompanying declaration of Dr. Miriam Frieden shows, such molecules can have advantages.

As Dr. Frieden explains, the effect of the presence of a deoxynucleotides (DNA) at the 3' end of an oligonucleotide rather than a beta-D-oxy –LNA (LNA) was examined using two pairs of oligonucleotides. As detailed below, all four of the oligonucleotides in the two pairs had the same sequence and length are were targeted to luciferase. The four oligonucleotides were tested for their ability to reduce luciferase expression in HeLa cells using the experimental protocol described below. One pair of oligonucleotides (Oligo A and Oligo B), depicted below, was identical in sequence, length and internucleotide linkages. They differed in that one member (Oligo A) had a LNA at the 3' terminus and in the other member (Oligo B) had a non-locked nucleotide (a DNA) at the 3' terminus.

	Luciferase expression	
	50 nM oligo	2 nM
Control Oligo $t_st_sc_sc_sg_st_sc_sa_st_sc_sg_st_sc_st_st_st$	29.8±4.7	65.8±8.1
Oligo A $T_sT_sC_sc_sg_st_sc_sa_st_sc_sg_st_sC_sT_sT_sT$	0.7±0.2	3.0±1.0
Oligo B $T_sT_sC_sc_sg_st_sc_sa_st_sc_sg_st_sC_sT_sT_st$	1.8±0.1	2.2±0.4

Capital Letters = oxyLNA; Lowercase Letters = DNA; s = phosphothioate bond, otherwise phosodiester bond

As Dr. Frieden states, when these oligonucleotides were tested for their ability to reduce expression of a target gene, luficerase, it was found in the oligonucleotide (Oligo B) having a

DNA at its 3' end was about as potent than the otherwise identical oligonucleotide (Oligo A) having a LNA at its 3' end. As LNA are known to bind to RNA with higher affinity than does DNA, one would expect that reduction in LNA would significantly reduce the potency of Oligo B compared to Oligo A.

Dr. Frieden goes on to explain that the other pair of oligonucleotides (Oligo C and Oligo D), depicted below, was identical in sequence and length (and identical in sequence and length to Oligos A and B above). However, one member (Oligo C) had a LNA at the 3' terminus and in the other member (Oligo D) had a non-locked nucleotide (a DNA) at the 3' terminus.

	Luciferase expression	
	50 nM oligo	2 nM oligo
Oligo C $TTCc_sg_st_sc_sa_st_sc_sg_st_sCTTT$	7.1±0.4	10.7±1.5
Oligo D $TTCc_sg_st_sc_sa_st_sc_sg_st_sCTT_st$	0.2±0.1	1.1±0.4

Capital Letters = oxyLNA; Lowercase Letters = DNA; s = phosphothioate bond, otherwise phosphodiester bond

In this pair, where there are fewer phosphothioate bonds, the oligonucleotide with a DNA at its 3' end (Oligo D) was more potent than the oligonucleotide having an LNA at it 3'. This is a surprising result given the greater affinity of LNA than DNA for complementary RNA. Importantly, the oligonucleotide (Oligo D) with the DNA at the 3' end was more potent than the oligonucleotide having a LNA at the 3' end (Oligo C). In fact, by comparing Oligo D and Oligo A, above, it can be seen that Oligo A which has a DNA at the 3' end and 10 phosphothioate bonds is more potent than Oligo A having a DNA at the 3' end and 15 phosphothioate bonds. This is a very important advantage of the oligonucleotide having a DNA at the 3' end because phosphothioate bonds are understood to confer a degree of toxicity and it is considered desirable to reduce the number of phosphothioate bonds.

Dr. Frieden states that these experiments demonstrate that by placing a DNA rather than a LNA at the 3' end of a gapmer oligonucleotide it is surprisingly possible to create an oligonucleotide that is more potent than an oligonucleotide of the same length and sequence, but containing more phosphothioate bonds.

These studies that are presented in the Declaration of Miram Frieden are evidence of unexpected advantages of certain oligonucleotides within the present claims and support the non-obviousness of the present claims.

V. Conclusion

Based on the foregoing, the Applicants request the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

Please apply any charges or credits to deposit account 06-1050 referencing Attorney Docket 22460-0010001.

Respectfully submitted,

Date:9 March 2008

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